REMARKS

Applicants want to thank the Examiner for the courtesy of conducting an interview with applicants' representative.

Claims 9 and 11 are in this application. Claims 1-8 and 10 have been cancelled. Claim 9 has been amended to replace the phrase "consisting essentially of" with "consisting of".

The examiner rejects Claims 9 and 11 as being anticipated under 35 USC 102 (a) and e)) in view of US 6,231,536. This is respectfully traversed.

US 6,231,536 is directed to a treatment method for cancers with ultrapheresis procedures to stimulate the patient's immune system to attack solid tumors. The Applicant has limited the term "comprising" of Claim 9 to "consisting of" so that the claimed method merely includes administration of thalidomide. Furthermore, as shown in Example 1 of the '536 patent, there was a reduction in the number and size of lung metastases when a patient received 24 ultrapheresis procedures. Example 4 of the patent describes treatment of a patient with metastic adenocarcinoma who was treated with 15 ultrapheresis procedures and thalidomide. Apparently, the treatment of adenocarcinoma results from the ultrapheresis in combination with thalidomide rather than thalidomide *per se* only. In addition, anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991). Since amended Claim 9 does not include each and every element of US patent 6,231,536, claims 9 and 11 are novel and it is respectfully requested that the rejection of claims 9 and 11 be

withdrawn.

The examiner rejects Claims 9 and 11 as being obvious in view of US 5,629,327, Masiero et al and US patent 5,696,092. The Applicants respectfully traverse this rejection.

The present invention relates to the use of thalidomide per se for treating hepatocellular carcinoma. Examples 2 and 3 illustrate a thalidomide treatment to patients having hepatocellular carcinoma, and show that oral administration of a capsule containing thalidomide as a single principle ingredient significantly reduces the tumor size and/or the serum level of alpha-fetoprotein in the patients.

The standard test used to establish *prima facie* obviousness is the test set out by the Supreme Court in *Graham v. John Deere* (383 US 1, 148 USPQ 459 (1966)). To determine whether a claim is *prima facie* obvious

1) the scope and content of the prior art are to be determined;

2) the differences between the prior art and the claims at issue are to be ascertained; and

3) the level of ordinary skill in the pertinent art resolved.

In addition, according to MPEP 2141, citing *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986), when applying 35 USC 103, the following tenets of patent law must be adhered to:

1) the claimed invention must be considered as a whole;

2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

Reasonable expectation of success is the standard with which obviousness is determined. *In re Merck & Co., Inc.*, 800 F.2d109, 231 USPQ 375 (Fed. Cir. 1986).

The reason, suggestion or motivation to combine references may be found explicitly or implicitly. While the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be clear and particular. *Ruiz v. A.B. Chance Co.,* 57 USPQ2d 1161 (Fed. Cir. 2000).

The scope and content of the cited art is discussed below:

US 5,629,327 is directed to a group of compounds (including thalidomide) having anti-angiogenesis activity. The citation illustrates the use of thalidomide in the treatment of corneal neovascularization and suggests some diseases involving undesired angiogenesis, such as rheumatoid and hemangiomas, treatable by thalidomide. Since no examples of solid tumors are given in the citation and there is no specific disclosure concerning the use of thalidomide to treat solid tumors in the citation, the citation does not provide one with a reasonable expectation of success that thalidomide can be used to treat liver cancer.

Masiero *et al.* discloses that thalidomide is currently tested in phase II of clinical trials for prostate cancer, glioblastoma and breast cancer. However, the citation does not suggest or imply the treatment of hepatocellular carcinoma by thalidomide as emphasized in the present invention. It is well known in the art that the treatment of a type of cancer does not mean that the same treatment will work for all types of solid tumors. For example, as indicated in Paragraph 9 of the article obtained from the website

www.netwellness.com/healthtopics/cancer/solid.cfm <http://www.netwellness.com/healthtopics/cancer/solid.cfm>, some tumors of the breast, uterus and prostate grow faster in the presence of certain hormones. Based on the teachings of the article, because of the differences in sensitivity to sex hormones of the breast and prostate hormones, the disclosures in Masiero of treatment of breast and prostate cancer do not teach treatment of liver cancer.

US 5,696,092 focuses on the use of compounds that inhibit arachidonic acid released by cells of a tumor for preventing metastasis of the tumor. The citation teaches that additional therapeutic agents such as angiogenesis inhibitors can be used in combination with the arachidonic acid release inhibitors, but does not provide any hint concerning the treatment of hepatocellular carcinoma by using thalidomide as disclosed in the invention.

As stated above the claimed invention is directed to the use of thalidomide to treat hepatocellular cancer.

It would not be obvious to one of ordinary skill in the art and one of ordinary skill in the art would not have a reasonable expectation of success based on the cited references of a method for treating hepatocellular carcinoma comprising administering to a patient in need thereof a pharmaceutical composition consisting of thalidomide as a single principle ingredient in an amount of 30 to 1200 mg and a pharmaceutically acceptable carrier.

The cited references in combination, do not render the current claims 9 and 11 obvious. The rejection under 35 USC 103 must be withdrawn.

Accordingly, applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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Cancer

How Solid Tumors Differ from One Another

Solid tumors are the tumors that usually come to mind when someone hears the word cancer. They arise in tissues other than the blood-related tissues. Solid tumors also have gene changes, but they tend to be different and more extensive than those seen in leukemias and lymphomas. For example, while leukemia can sometimes result from a single cytogenetic abnormality like the 9;22 translocation, the development of solid tumors usually involves a smorgasbord of genetic changes. These include the activation of one or more oncogenes together with the inactivation of one or more tumor suppressor genes.

Oncogenes are normal genes that are involved in regulating cell division. These normal genes become oncogenes when mutations cause the genes to run when they shouldn't be or run faster than they should.

Tumor suppressor genes are genes that block or prevent inappropriate cell division. This can include the drastic step of triggering the cell to self-destruct when the cell's DNA is badly damaged by mutations. This process of self-destruction is known as programmed cell death, or apoptosis. When mutations disable tumor suppressor genes themselves, these safeguards are lost, enabling a cell to divide when it shouldn't or live longer than it should. Both are important characteristics of cancer cells.

A third group of genes that play an important role in cancer are those that produce DNA repair enzymes. DNA repair enzymes cut out and replace sections of DNA—of a gene—damaged by cancer-causing chemicals, oxygen radicals, or ultraviolet light (in skin cells), or that were duplicated improperly prior to cell division. When mutations disable these genes, damaged DNA isn't repaired as effectively, allowing mutations to accumulate more quickly.

Mutations occur daily in cells for a variety of reasons, and the laws of statistics tell us that eventually some will occur that are cancer-related. If repair enzymes are not working, that damage won't get corrected, and we're off to the races. (Some people are born with faulty genes for DNA repair enzymes, resulting in a higher incidence of certain cancers in these individuals. This is the basis for some hereditary cancers.)

Once a mutation occurs in a cell, it not only weakens the cell's ability to control its growth, but it allows other damage to follow more easily. One hit makes the cell sensitive to subsequent hits. That's why one cell progresses to cancer while the other ones around it don't.

Solid tumors arise because mutations in oncogenes, tumor suppressor genes, and genes for DNA repair enzymes accumulate over time, often a decade or more. By the time the cell becomes malignant, the cytogenetics are bizarre. Instead of something like a single 8;21 translocation that we can see in a fraction of leukemia cases that we know will be sensitive to standard therapy, solid-tumor cells may undergo a multitude of cytogenetic or genetic changes, some of which may resist almost any standard therapy.

That may be why some solid tumors are especially difficult to treat. The likelihood of any one treatment being effective for tumors with such a host of diverse genetic changes is probably not very high. More research in human cancer genetics should help us better sort things out at the genetic level, and will likely improve treatments and ultimately survival.

Some solid tumors stand apart from others in still another way: some tumors of the breast, uterus, and prostate grow faster in the presence of certain hormones. Hormone-dependent prostate tumors are sensitive to male hormones known as androgens; hormone-dependent breast tumors are sensitive to the hormone estrogen; and hormone-dependent uterine tumors are sensitive to estrogens and progestrone.

The growth of hormone-dependent breast-cancer cells is stimulated by the interaction of estrogen with molecules called estrogen receptors, which are found in the nucleus of those cells. When estrogen is added to a culture of breast tumor cells

that have estrogen receptors, the cells grow; when the same cells are cultured without estrogen, they may almost stop growing.

Some breast tumors are composed of cells that lack estrogen receptors. Such hormone-independent breast tumors tend to grow faster than hormone-dependent tumors even in the presence of estrogen. When grown in the laboratory, hormone-dependent breast cancer cells double in number over several days. Hormone-independent cells, on the other hand, double in number in a day or two (for comparison, some lung or liver cancer cell have doubling times of 6 or 10 hours).

The presence of estrogen receptors in tumor cells provides an important therapeutic target. We can use the drug tamoxifen to block the receptors so that estrogen cannot bind to them and slow the growth of the tumor. Consequently, breast tumors are now routinely tested to determine if estrogen receptors are present (the tumor is then said to be ER positive) or absent (ER negative).

Hormone-dependent tumor cells are thought to retain some aspects of hormonal growth regulation seen in healthy breast cells. It may be that with the passage of time, mutations in ER-positive tumors cause the malignant cells to lose their sensitivity to estrogen and become hormone independent. This may represent a later stage in the progression of these malignancies.

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